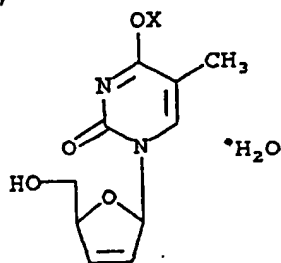


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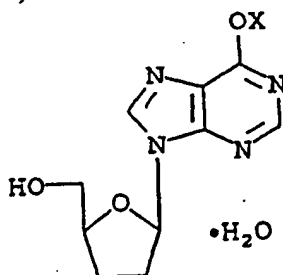
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(51) Int.Cl.⁶ C07H 19/04, A61K 31/70
(30) 1989/05/15 (352,065) US

- (54) **SELS CRISTALLINS STABLES DE MONOHYDRATE DE 2',3'-DIDESOXYINOSINE, DE MONOHYDRATE DE 2',3'-DIDESOXY-2',3'-DIDEHYDROTHYMIDINE, ET DE HEMIHYDRATE DE 2',3'-DIDESOXY-2'-FLUOROINOSINE, HAUTEMENT SOLUBLES DANS L'EAU ET ANTIVIRAUX**
(54) **ANTIVIRAL, HIGHLY WATER SOLUBLE, STABLE, CRYSTALLINE SALTS OF 2',3'-DIDESOXYINOSINE MONOHYDRATE, 2',3'-DIDESOXY-2',3'-DIDEHYDROTHYMIDINE MONOHYDRATE AND 2',3'-DIDESOXY-2'-FLUOROINOSINE HEMIHYDRATE**

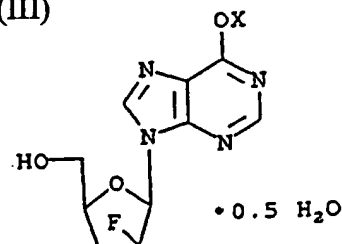
(I)



(II)



(III)



(57) Préparation de sels cristallisés stables, très hydrosolubles, de 2',3'-dideoxy-2',3'-didehydrothymidine de formule (voir formule I), de 2',3'-dideoxyinosine de formule (voir formule II), et de 2',3'-dideoxy-2'-fluoro-inosine de formule (voir formule III), où X est un cation organique ou minéral. Ces sels sont utiles comme agents antiviraux.

(57) Very highly water soluble, stable, crystalline salts of 2',3'-dideoxy-2',3'-didehydrothymidine of the formula (see formula I) 2',3'-dideoxyinosine of the formula (see formula II) and 2',3'-dideoxy-2'-fluoroinosine of the formula (see formula III) wherein X is an organic or inorganic cation are prepared. Such salts are useful as antiviral agents.



BACKGROUND OF THE INVENTION

Field of the Invention

The present invention concerns highly water soluble, stable, crystalline antiviral (including antiretroviral) salts of 2',3'-dideoxyinosine, 2',3'-dideoxy-2',3'-didehydrothymidine and 2',3'-dideoxy-2'-fluorinosine, particularly sodium salts thereof.

Background Information

Infectious viral diseases are recognized as an important medical problem. Progress against infectious viral disease requires the development of drugs with selective antiviral activity, while remaining benign to normal cell lines. A number of antiviral agents currently under study which seem to possess some selectivity are nucleoside analogs. In general, these compounds are structural analogs of the naturally occurring nucleosides. Structural modification in either the purine or pyrimidine base nucleus and/or the saccharide component results in a synthetically modified nucleoside derivative which, when incorporated into a viral nucleic acid forming process, acts to disrupt further synthesis of viral nucleic acid.

Effectiveness of these antiviral agents depends on selective conversion by viral enzymes, but not by host enzymes, to the corresponding nucleotide analog which is then

converted to the triphosphate followed by incorporation into viral nucleic acid. A problem with this antiviral strategy has been the emergence of certain viral strains whose enzymes poorly promote phosphorylation of the nucleoside analogs. To circumvent this problem, intact nucleotide analogs appear to be potentially quite useful as antivirals for incorporation into viral nucleic acid.

PCT application WO87/01284 to Mitsuya and Broder describes the use of 2',3'-dideoxyinosine for use against AIDS.

EP 273,277 to Lin and Prusoff discloses the use of 2',3'-dideoxy-2',3'-didehydrothymidine in treating patients infected with a retrovirus.

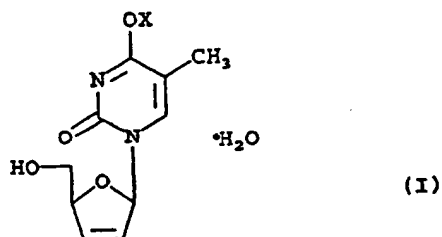
Erik De Clercq, "Potential Drugs for the Treatment of AIDS", Journal of Antimicrobial Chemotherapy, 23, Suppl. A, 35-46, (1989), describes the use of dideoxynucleoside analogues to inhibit the infectivity and cytopathic effect of human immunodeficiency virus (HIV).

EP 287,313 discloses 2',3'-dideoxy-2'-fluorinosine (F-ddI) and its activity against HIV.

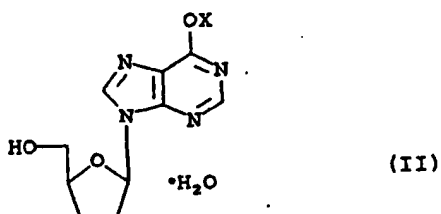
SUMMARY OF THE INVENTION

The present invention concerns very highly water soluble, stable, crystalline salts of 2',3'-dideoxy-2',3'-didehydrothy-

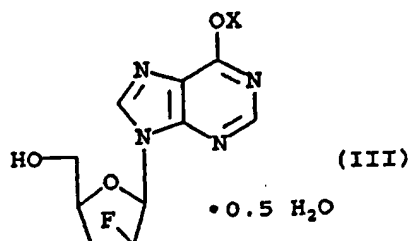
midine ("D4T") of the formula



2',3'-dideoxyinosine ("DDI")



and 2',3'-dideoxy-2'-fluoroinosine (F-ddI)



, wherein X is a cation, e.g., Na, K or Mg.

The present invention also concerns pharmaceutical compositions comprising an antiviral effective amount of such salts and a solid, liquid or gaseous physiologically acceptable diluent.

Still further, the present invention relates to a method of treating a warm blooded animal, for example, a human, comprising administering to such warm blooded animal an antiviral effective amount of one of the aforesaid salts.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts an IR for sodium-2',3'-dideoxyinosine.

Fig. 2 depicts a TGA for sodium-2',3'-dideoxyinosine.

Fig. 3 depicts a DSC for sodium-2',3'-dideoxyinosine.

Fig. 4 depicts a NMR for sodium-2',3'-dideoxyinosine.

Fig. 5 depicts an IR for sodium-2',3'-dideoxy-2',3'-didehydrothymidine.

Fig. 6 depicts a TGA for sodium-2',3'-dideoxy-2',3'-didehydrothymidine.

Fig. 7 depicts a DSC for sodium-2',3'-dideoxy-2',3'-didehydrothymidine.

Fig. 8 depicts X-ray data for sodium-2',3'-dideoxy-2',3'-didehydrothymidine.

Fig. 9 depicts an NMR for sodium-2',3'-dideoxy-2',3'-didehydrothymidine.

Fig. 10 depicts an IR for sodium-2',3'-dideoxy-2'-fluorinosine.

Fig. 11 depicts an NMR for sodium-2',3'-dideoxy-2'-fluorinosine.

Fig. 12 depicts a DSC for sodium-2',3'-dideoxy-2'-fluorinosine.

Fig. 13 depicts a TGA for sodium-2',3'-dideoxy-2'-fluorinosine.

DETAILED DESCRIPTION OF THE INVENTION

As indicated above, the present invention pertains to pharmaceutically acceptable non-toxic salts of 2',3'-dideoxyinosine, 2',3'-dideoxy-2',3'-didehydrothymidine and 2',3'-dideoxy-2'-fluorinosine containing, for example, Na⁺, Li⁺, K⁺, Ca⁺⁺ and Mg⁺⁺. Such salts may include organic cations and also those containing an appropriate cation such as an alkali or alkaline earth metal ion or an ammonium or a quaternary amino ion. The preferred salt is the sodium salt. Metal salts can be prepared by reacting the metal hydroxide with 2',3'-dideoxyinosine, 2',3'-dideoxy-2',3'-didehydrothymidine or 2',3'-dideoxy-2'-fluorinosine. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal ion.

The compounds of this invention have desirable antiviral activity. They exhibit activity against viruses, for example, Herpes Simplex virus I, Herpes Simplex virus II, cytomegalovirus, Varicella Zoster virus, influenza virus, vaccinia, polio, rubella, smallpox, cowpox, Epstein-Barr virus, measles virus, human respiratory virus, papillomavirus and Sinbis virus, just to mention a few and also against retroviruses, for example, virus of human immunodeficiency (HIV).

As mentioned above, the compounds of the present invention are useful active ingredients in human and veterinary medicine for the treatment and prophylaxis of diseases caused

by retroviruses. Examples of fields of indication in human medicine regarding retroviruses are as follows:

- (1) the treatment or prophylaxis of human retrovirus infections;
- (2) the treatment or prophylaxis of diseases caused by HIV (virus of human immunodeficiency; previously called HTLV III/LAV or AIDS) and the stages associated therewith such as ARC (AIDS related complex) and LAS (lymph adenopathy syndrome) and the immune weakness and encephalopathy caused by this retrovirus;
- (3) the treatment or prophylaxis of HTLV I infection or HTLV II infection;
- (4) the treatment or prophylaxis of the AIDS carrier state (AIDS transmitter state); and
- (5) the treatment or prophylaxis of diseases caused by hepatitis B virus.

Examples of indications in veterinary medicine are as follows:

- (1) Maedivisna (in sheep and goats),
- (2) progressive pneumonia virus (PPV) (in sheep and goats),
- (3) caprine arthritis encephalitis virus (in sheep and goats),
- (4) Zwoegerziekte virus (in sheep),

- (5) infectious virus of anemia (of the horse), and
- (6) infections caused by cat leukemia virus.

For use against viral infections the compounds of this invention can be formulated into pharmaceutical preparations. Such preparations are composed of one or more of the inventive compounds in association with pharmaceutically acceptable carriers. The reference Remington's Pharmaceutical Sciences, 17th Edition, A.R. Gennaro, editor (Mack Publishing Company, 1985) discloses typical carriers and methods of preparation.

The compounds of the invention are administered systemically to warm blooded animals, e.g., humans. By systemic administration is intended oral, rectal, and parenteral (i.e., intramuscular, intravenous, subcutaneous and nasal) routes. Generally, it will be found that when a compound of the present invention is administered orally, a larger quantity of the reactive agent may be required to produce the same effect as the smaller quantity given parenterally. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level that will produce an effective antiviral effect without causing any harmful or untoward side effects.

Therapeutically and prophylactically the instant compounds are usually given as pharmaceutical compositions comprised of an effective antiviral amount of a compound according to the invention and one or more pharmaceutically acceptable carriers, as stated hereinabove. Pharmaceutical compositions for effecting such treatment will contain a major or minor amount, e.g., from 100 to 0.5% of at least one compound of the present invention in combination with a pharmaceutical carrier, the carrier comprising one or more solid, semi-solid, or liquid diluents, fillers and formulation

adjuvants which are non-toxic, inert and pharmaceutically acceptable.

Such pharmaceutical compositions are preferably in dosage unit form; i.e., physically discrete units containing a predetermined amount of the drug corresponding to a fraction or multiple of the dose which is calculated to produce the desired therapeutic response. Other therapeutic agents can also be present.

Pharmaceutical compositions providing from about 50 mg to 2 grams of the active ingredient per unit dose are preferred and are conventionally prepared as tablets, lozenges, capsules, powders, granules, aqueous or oily suspensions, syrups, elixirs, and aqueous solutions. Preferred oral compositions are in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g., syrup, acacia, gelatin, sorbitol, tragacanth or polyvinylpyrrolidone), fillers (e.g., lactose, sugar, corn starch, calcium phosphate, sorbitol, or glycine), lubricants (e.g., magnesium stearate, talc, polyethylene glycol or silica), disintegrants (e.g., starch), buffering agents (inorganic or organic) and wetting agents (e.g., sodium lauryl sulfate). Solutions or suspensions of an inventive compound with conventional pharmaceutical vehicles are employed for parenteral compositions, such as an aqueous solution for intravenous injection or an oily suspension for intramuscular injection. Such compositions having the desired clarity, stability and adaptability for parenteral use are obtained by dissolving from 0.1% to 35% by weight of an active inventive compound in water or a vehicle comprising a polyhydric aliphatic alcohol such as glycerine, propylene glycol, and polyethylene glycol or mixtures thereof. The polyethylene glycols comprise a mixture of non-volatile, usually liquid, polyethylene glycols which are soluble in both

water and organic liquids and have molecular weights from about 200 to 1500.

The inventive compounds are prone to acid hydrolysis. For optimum bioavailability, tablets, capsules and granules required for oral dosage should be enteric coated, strongly buffered against gastric acid, or both.

The salts of this patent application are stable, crystalline and of very high water solubility (> 300 mg/ml), ideally suited for high concentration, low volume IV-IM injectables. Most importantly, the high alkalinity (pH 9.5-11) of these new and novel salts allow for self-buffering against gastric acid. Thus, less buffer could be required in oral dosage forms.

The salts of the invention are reversibly "immobilized" in the enolic form, and thus, can be considered as intermediates for synthesis of varied potentially bio-active derivatives as enol esters (prodrugs) and enol ethers. The esters and ethers could also function as protecting (blocking) groups, allowing for synthetic work on other functions or moieties of the molecules.

Considering the biological activities possessed by the compounds of the instant invention, it can be seen that these compounds have antiviral properties, particularly suited to their use in combating viral infections. Thus, another aspect of the instant invention concerns a process for treating viral (including retroviral) infections in a mammal in need of such treatment which comprises systemic administration to such mammal of an effective dose of an inventive compound.

On the basis of testing, an effective dose could be expected to be from about 0.1 to about 5 mg/kg body weight with about 1 to about 4 mg/kg body weight a preferred dosage.

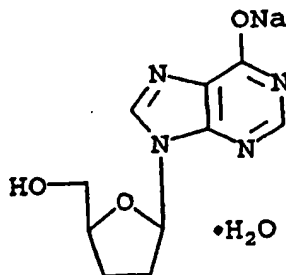
range. It is envisioned that for clinical antiviral application, compounds of the instant invention will be administered in the same manner as for the reference drug zidovudine (AZT). For clinical applications, however, the dosage and dosage regimen must in each case be carefully adjusted, utilizing sound professional judgement and consideration of the age, weight and condition of the recipient, the route of administration and the nature and gravity of the illness. Generally a daily oral dose will comprise from about 150 mg to about 5 grams, preferably 50-1500 mg of an inventive compound administered from one to three times a day. In some instances, a sufficient therapeutic effect can be obtained at lower doses, while in others, larger doses will be required.

Description of the Specific Embodiments

The compounds which constitute this invention and their methods of preparation will appear more fully from a consideration of the following examples which are given for the purpose of illustration only and are not to be construed as limiting the invention in sphere or scope. All temperatures are understood to be in degrees C when not specified. All compounds gave satisfactory elemental analyses.

Example 1

Preparation of Sodium-DDI Monohydrate



MW: DDI = 236.14

MW: NaOH = 40

$$\frac{1 \text{ g DDI}}{236.14} = \frac{x}{40} = \frac{169 \text{ mg NaOH}}{40} = 4.3 \text{ ml of 1N-NaOH is equivalent to 1 g of DDI for a 1/1 molar ratio.}$$

1. Add 1 g of DDI to 4.51 ml of aqueous 1N-NaOH (1.05 molar equivalents with moderate stirring at 10-25°C over a 5 minute interval. A solution (pH 9.5 - 11), or near solution is obtained.
2. If required, pass the solution through the equivalent of a 0.2 - 0.45 micron Gelman HT-Tuffryn filter to clarify.

Steps 1 and 2 should be completed within 1.5 hours.

3. Add the Na-DDI solution, over a 10-15 minute interval to 50-75 ml of very vigorously stirred isopropanol (alternatively, acetone could be used). Crystals form. Continue vigorous stirring (closed system) for 2 hours.
4. Collect the crystals via a suitable vacuum filtration procedure. Do not draw excess air through the filter-cake. Tamp the crystalline filter-cake (under vacuum) to remove any cracks or fissures which may form. Do not draw excess air through the cake.
5. Wash the filter-cake with three separate 15 ml portions of isopropanol and then with three separate 20 ml portions of acetone. Do not draw excess air through the filter-cake between washings. Remove any cracks or fissures which may form between washings by tamping.

6. High vacuum dry the crystals at 24-35°C for 24 hours.
Expected yield: 1-1.1g.
7. If desired, acetone can be totally substituted for the preferred isopropanol and the modes of addition reversed, if desired viz, the solvents added to the stirring aqueous DDI solution over a half-hour interval.

KOH and/or other strong organic and inorganic bases can be substituted for NaOH to form the corresponding salts.

Chemical and Physical Properties Obtained for Na-DDI·H₂O

1. Water Solubility: >300 mg/ml (pH 9.5-11)
2. Aqueous Solution Stability: 5% loss for 1 week at 50°C;
10% loss for 1 week at 70°C
3. Solid State Stability: No loss for 5 weeks at 70°C
4. Elemental Analysis: C₁₀H₁₁N₄O₃Na·H₂O (C₁₀H₁₃N₄O₄Na)
MW - 276.26

	<u>Theory</u>	<u>Found</u>
% C	43.5	43.18
% H	4.7	4.6
% N	20.3	20.16
% Na (Ash)	8.3	8.26
% H ₂ O KF	6.5 (for monohydrate)	6.57
5. <u>IR:</u>	See Fig. 1	
6. <u>TGA:</u>	See Fig. 2	
7. <u>DSC:</u>	See Fig. 3	
8. <u>X-Ray (film):</u>		

X-Ray d-Lines

<u>DDI</u>			<u>Na-DDI H₂O</u>		
<u>d</u>		<u>I/I₀</u>	<u>d</u>		<u>I/I₀</u>
14.57	-	100	8.75	-	60
8.39	-	80	7.82	-	80
7.46	-	20	6.21	-	30
6.60	-	10	5.81	-	20
6.00	-	20	5.28	-	10

DDI

<u>d</u>	<u>I/Io</u>
5.50 -	20
5.14 -	20
4.79 -	30
4.46 -	30
3.54 -	90
3.21 -	40
3.04 -	30

Na-DDI H₂O

<u>d</u>	<u>I/Io</u>
5.00 -	10
4.65 -	40
4.22 -	50
3.89 -	100
3.49 -	20
3.25 -	20
3.09 -	10
2.92 -	50
2.77 -	10
2.61 -	20

9. NMR: See Fig. 4 (no solvents present)

Table IHPLC Assay Method

Column:

IBM Phenyl, 5 micron, 4.5 x 150 nm

Mobile Phase:

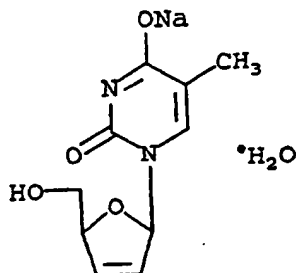
98% 0.015M NH₄H₂PO₄ in Milli-Q Water,
pH 7.1 with concentrated NH₄OH/2%
acetonitrile

Flow Rate:

0.1 mg/ml in water

Approximate Retention
Times:

ddI: 10 minutes
Hypoxanthine: 3 minutes

Example 2Preparation of Sodium-D₄T HydrateMW: D₄T = 224.2

MW: NaOH = 40

$$\frac{1 \text{ g D}_4\text{T}}{224.21} = \frac{x}{40} = \frac{178.4 \text{ mg NaOH}}{40} = 4.46 \text{ ml of 1N-NaOH is equivalent to 1 g of D}_4\text{T for a 1/1 molar ratio.}$$

1. Add 1 g of D₄T to 4.7 ml of aqueous 1N-NaOH (1.05 molar equivalents) with moderate stirring at 15-25°C over a five minute interval. A solution (pH 9.5 - 11) or near solution is obtained.
2. Repeat and follow Steps 2-7 as described in Example 1 for the preparation of Na-DDI H₂O.
3. Expected yield of D₄T·H₂O = 1 - 1.1 g.

Chemical and Physical Parameters Obtained for Na-D₄T·H₂O

1. Water Solubility: > 300 mg/ml (pH 9.5 - 11)
2. Aqueous Solution Stability: 1 week at 50°C-20% remaining
3. Solid State Stability: No loss for 1 week at 70°C
4. Elemental Analysis: C₁₀H₁₁N₂O₄Na·H₂O (C₁₀H₁₃N₂O₅Na)

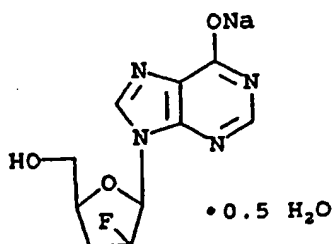
MW: 264.22

	<u>Theory</u>	<u>Found</u>
% C	45.5	45.05
% H	5.0	4.89

% N	10.6	10.37
% Na	8.7	8.43
% H ₂ O KF	6.8 (for monohydrate)	6.9
5. <u>IR:</u>	See Fig. 5	
6. <u>TGA:</u>	See Fig. 6	
7. <u>DSC:</u>	See Fig. 7	
8. <u>X-Ray:</u>	See Fig. 8	

HPLC Assay Method

Column:	IBM Phenyl, 5 micron, 4.5 x 150 nm	
Mobile Phase:	98% 0.015M NH ₄ H ₂ PO ₄ in Milli-Q Water, pH 7.1 with concentrated NH ₄ OH/2% acetonitrile	
Flow Rate:	0.1 ml/minute	
Injection Volume:	25 microliter	
Run Time:	20 minutes	
Wavelength:	254 nm	
Temperature:	ambient, 20-30°C	
Sample Conc.:	approximately 0.1 mg/ml in water	
Approximate Retention Times:	d4T:	8 minutes
	Thymine:	3 minutes

Example 3Preparation of Sodium F-ddI Hemihydrate

MW: FDDI = 254.24

MW: NaOH = 40

$$\frac{436 \text{ mg FDDI}}{254.24} = \frac{x}{40} = \frac{68.6 \text{ mg NaOH}}{40} = 1.72 \text{ ml NaOH is equivalent to 436 mg of FDDI for a 1:1 molar ratio}$$

1. FDDI (426 mg) was slurried in 1.8 ml of 1N NaOH (256 mg/ml NaFDDI). A pH 9.9 solution was obtained in 2 minutes.
2. Two ml of isopropanol was added. The solution remained clear.
3. Isopropanol was slowly added with slurring. Heavy needle-like crystallization started when 15 ml of isopropanol was added. The mixture was slurried for 10 minutes.
4. Fifteen ml of acetone was added and the mixture was slurried an additional 15 minutes.
5. The crystals were removed by vacuum filtration, washed with 15 ml of acetone and 20 ml of ether, and vacuum-dried (P_2O_5 at $50^\circ C$ for 2 hours and then at $24^\circ C$ for 24 hours). Yield: 430 mg.

A 21 mg sample readily dissolved in 0.05 ml of water (= 400 mg/ml; pH 10.0).

Elemental Analysis: $C_{10}H_{10}N_4FO_3Na$

	<u>Theory</u>	<u>Found</u>
% C	42.0	41.19
% H	3.9	3.73
% N	19.6	18.8
% F	6.6	6.13
% Na	8.0	8.11
% H_2O KF	3.23 (hemihydrate)	3.23

X-Ray (film):X-Ray d-Lines

<u>d</u>	<u>I/I₀</u>
16.20	50
9.40	50
6.91	50
5.81	50
5.40	100

NMR: See Fig. 11. Data consistent with proposed structure.
No acetone or ether present. No α -isomer present.

IR: See Fig. 10.

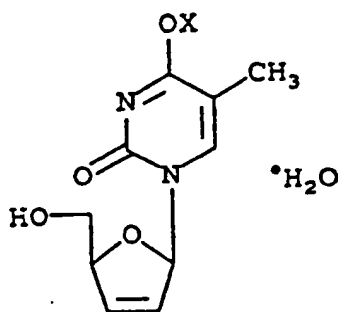
TGA: See Fig. 13.

DSC: See Fig. 12.

It will be appreciated that the instant specification and claims are set forth by way of illustration and not limitation, and that various modifications and changes may be made without departing from the spirit and scope for the present invention.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A highly water soluble, stable, crystalline salt of 2',3'-dideoxy-2',3'-didehydrothymidine of the formula



wherein X is an inorganic cation.

2. The salt according to claim 1, wherein X is an alkali or alkaline earth metal ion or an ammonium or a quaternary amino ion.

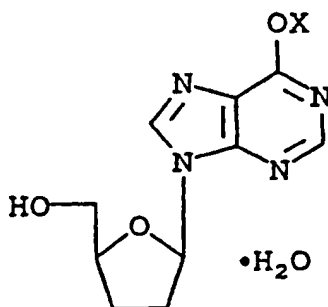
3. A salt according to claim 1, wherein X is Na.

4. A pharmaceutical composition comprising an antiviral effective amount of a salt according to claim 1, 2 or 3 and a physiological acceptable solid or liquid diluent.

5. The use of an antiviral effective amount of a salt according to claim 1, 2 or 3, either alone or in admixture with a diluent or in the form of a medicament for treating a warm blooded animal with a virus wherein said virus is susceptible to treatment by said salt.

6. The use of claim 5 wherein the salt is a medicament in the form of a tablet, capsule or powder for oral administration and is enteric coated and buffered against gastric acid.

7. A highly water soluble, stable, crystalline salt of 2',3'-dideoxyinosine of the formula



wherein X is an inorganic cation.

8. The salt according to claim 7, wherein X is an alkali or alkaline earth metal ion or an ammonium or a quaternary amino ion.

9. A salt according to claim 7, wherein X is sodium.

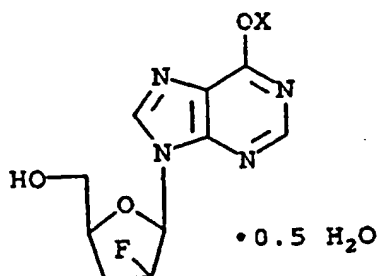
10. A pharmaceutical composition comprising an antiviral effective amount of a salt according to claim 7, 8 or 9 and a physiologically acceptable solid or liquid diluent.

11. The use of an antiviral effective amount of a salt according to claim 7, 8 or 9, either alone or in admixture with a diluent or in the form of a medicament for treating

a warm blooded animal with a virus wherein said virus is susceptible to treatment by said salt.

12. The use of claim 11, wherein the salt is a medicament in the form of a tablet, capsule or powder for oral administration and is enteric coated and buffered against gastric acid.

13. A highly water-soluble, stable, crystalline salt of 2',3'-dideoxy-2'-fluorinosine of the formula



wherein X is an inorganic cation.

14. The salt according to claim 13, wherein X is an alkali or alkaline earth metal ion or an ammonium or a quaternary amino ion.

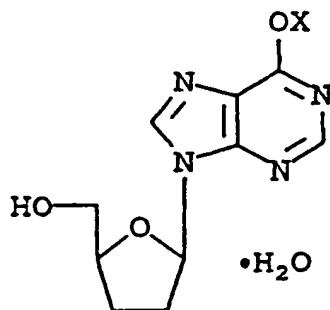
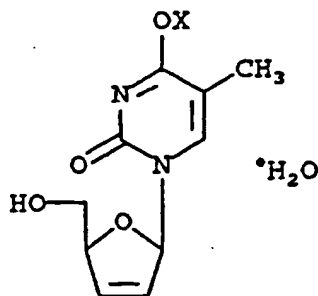
15. A salt according to claim 13, wherein X is Na.

16. A pharmaceutical composition containing an antiviral effective amount of a salt according to claim 13, 14 or 15 and a pharmaceutically acceptable carrier.

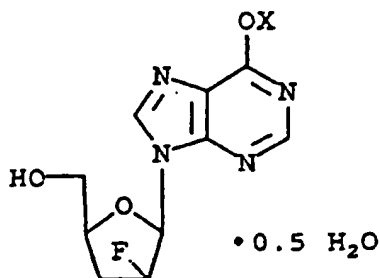
17. The use of an antiviral effective amount of a salt according to claim 13, 14 or 15, either alone or in admixture with a diluent or in the form of a medicament for treating a warm blooded animal with a virus wherein said virus is susceptible to treatment by said salt.

18. The use of claim 17 wherein the salt is a medicament in the form of a tablet, capsule or powder for oral administration and is enteric coated and buffered against gastric acid.

19. A process for the preparation of a stable, crystalline, water-soluble salt of the formula



or



wherein X is an inorganic cation, which comprises reacting 2',3'-dideoxy-2',3'-didehydrothymidine, 2',3'-dideoxyinosine or 2',3'-dideoxy-2'-fluoroinosine in an inert aqueous solvent system with an appropriate base providing the desired inorganic cation and allowing the desired salt to crystallize from the solution.

20. The process according to claim 19, wherein X is an alkali or alkaline earth metal ion or an ammonium or a quaternary amino ion.

21. The process according to claim 19, wherein X is Na.

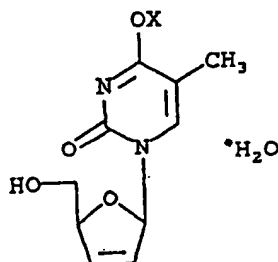
Barrigar & Moss
81 Metcalfe Street, 7th Floor
Ottawa, Ontario
K1P 6K7

Agents for the Applicant

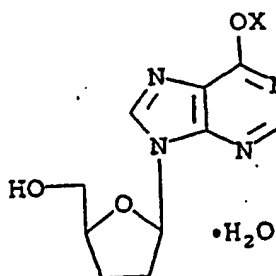
2016765

ABSTRACT OF THE DISCLOSURE

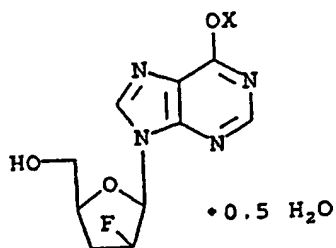
Very highly water soluble, stable, crystalline salts
of 2',3'-dideoxy-2',3'-didehydrothymidine of the formula



2',3'-dideoxyinosine of the formula



and 2',3'-dideoxy-2'-fluorinosine of the formula



wherein X is an organic or inorganic cation are prepared.
Such salts are useful as antiviral agents.

#2016765

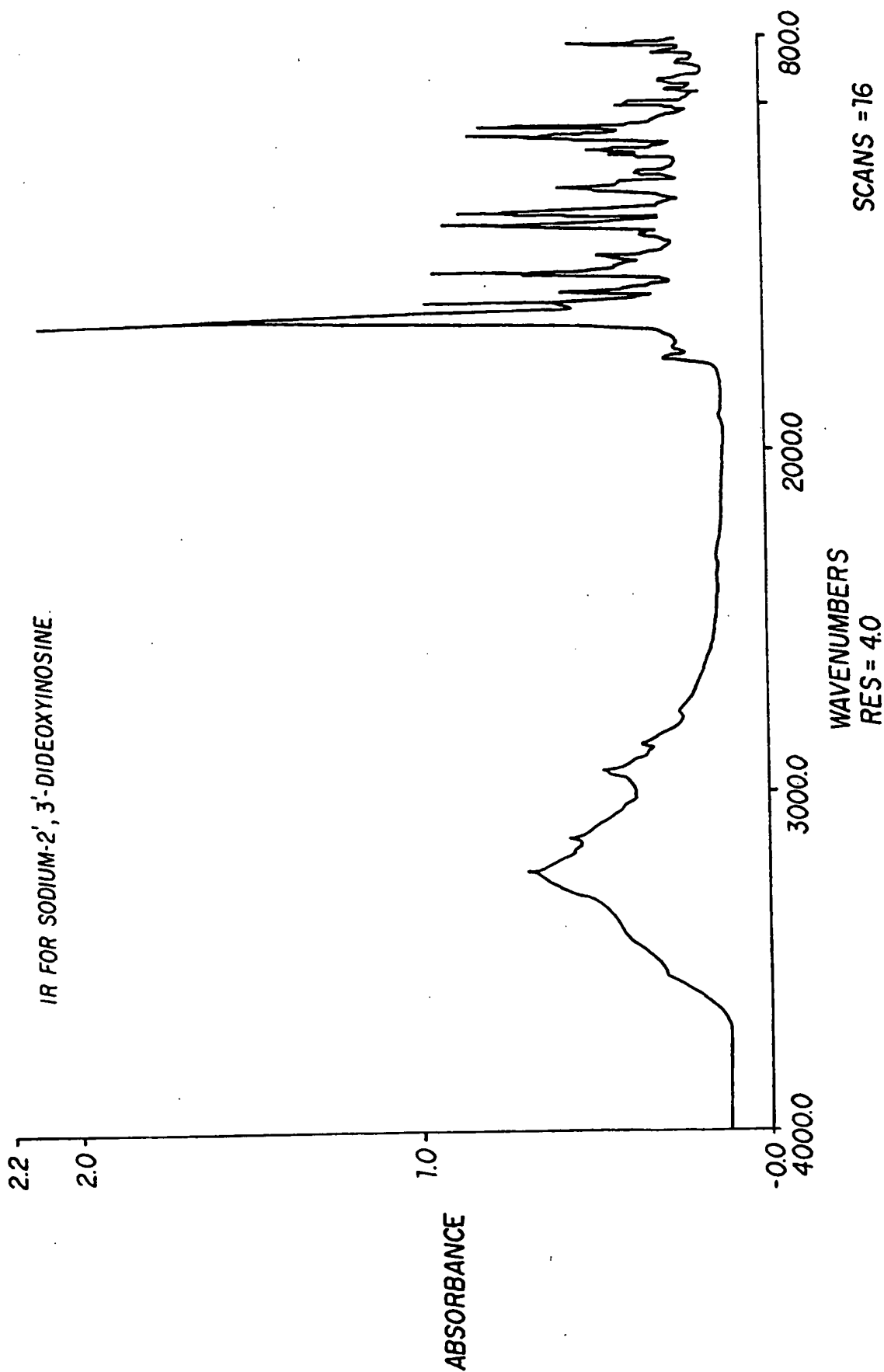


FIG. 1

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TGA FOR SODIUM-2',3'-DIDEOXYINOSINE.

7 SERIES THERMAL ANALYSIS SYSTEM

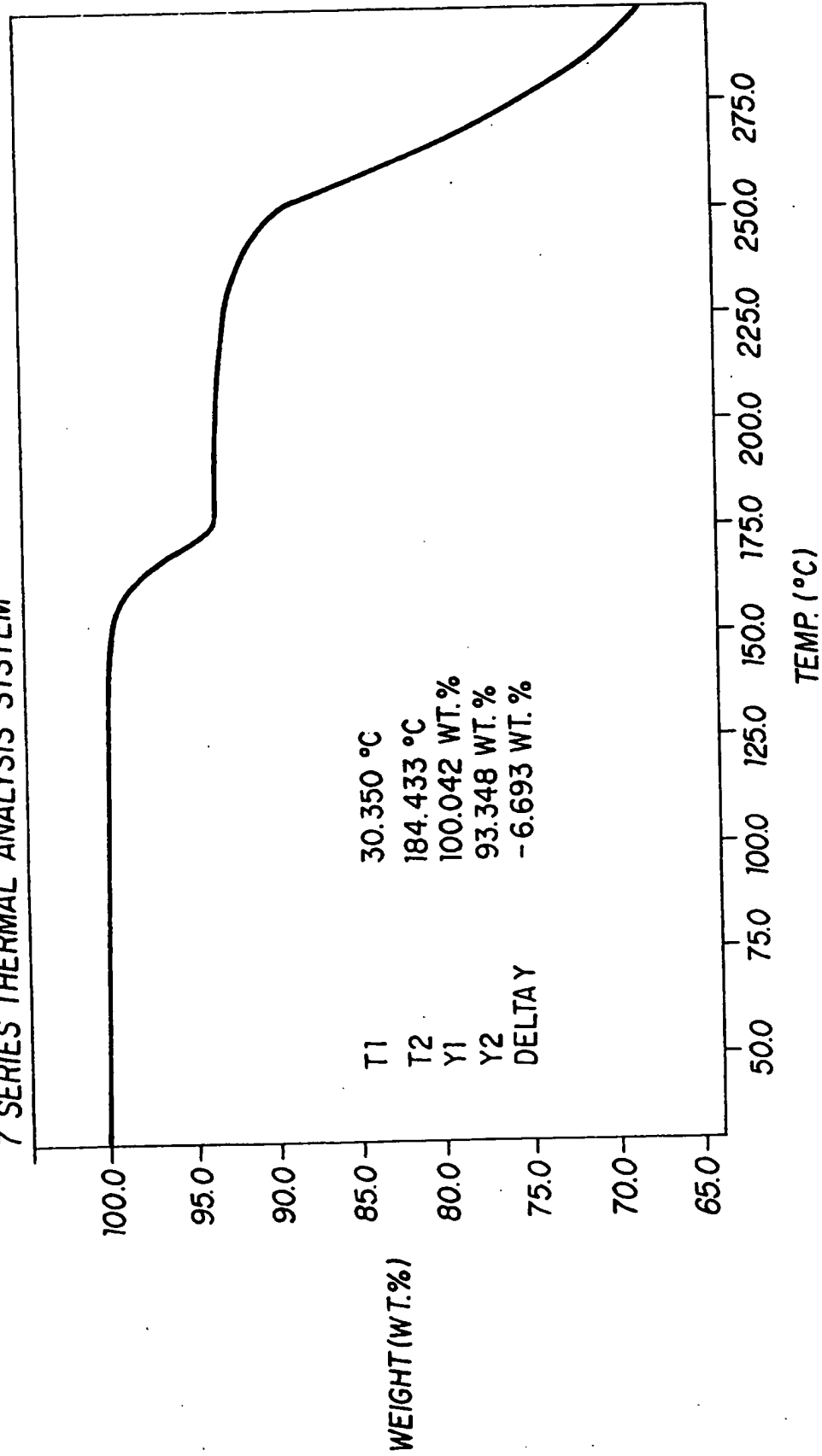


FIG. 2

Beaman & Co.

DSC FOR SODIUM-2',3'-DIDEOXYINOSINE.

7 SERIES THERMAL ANALYSIS SYSTEM

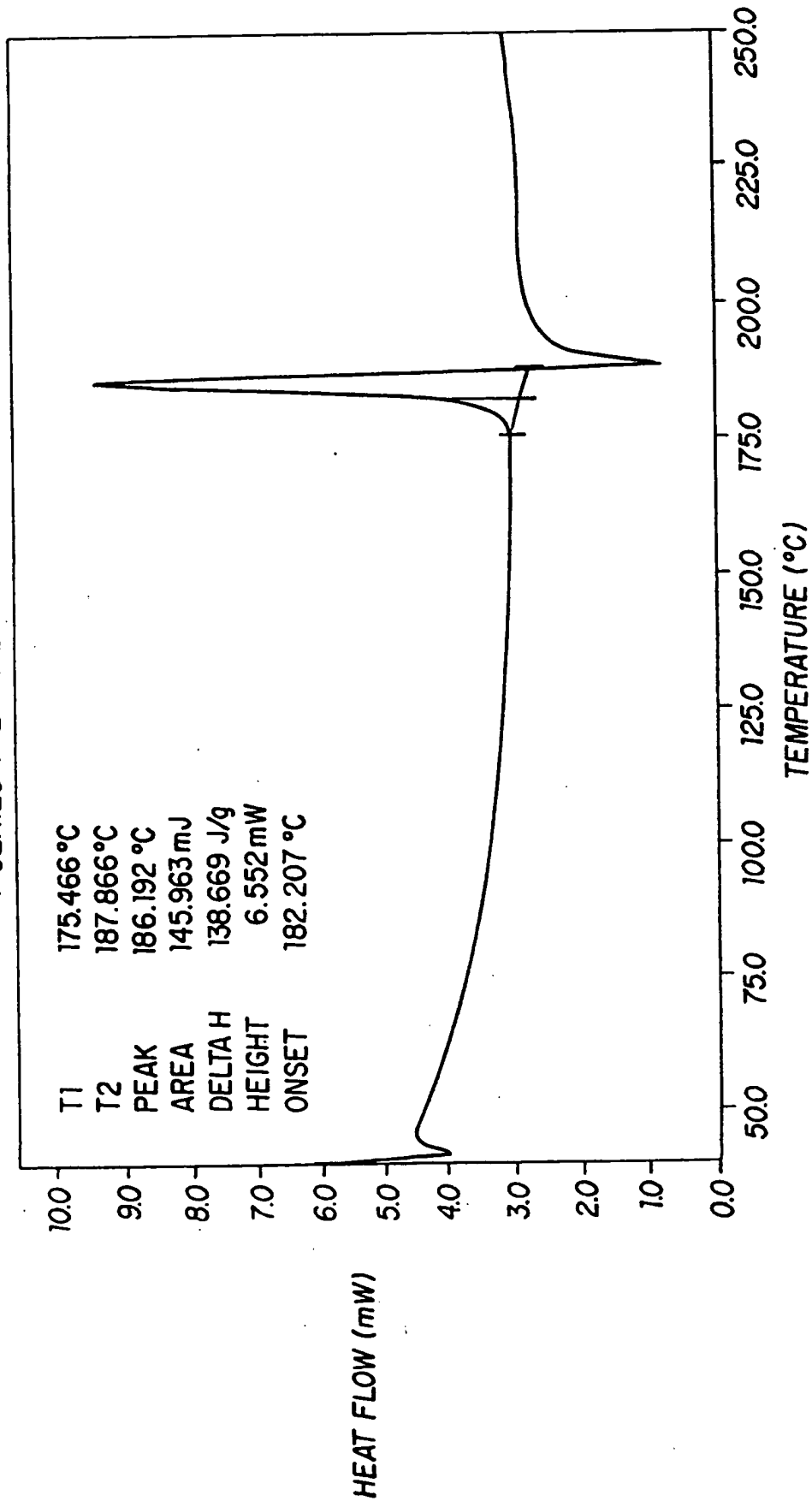


FIG. 3

HEAT FLOW (mW)

TEMPERATURE (°C)

~~BRUER~~

SA140S.106

AU PROG:

X45.AU

DATE 3-1-89

TIME 16:33

SOLVENT D2O

SF 360.135

SF0 360.130

O1 6632.751

SI 32768

TD 32768

SW 7246.377

HZ/PT .442

PW 0.0

RD 0.0

AQ 2.261

RG 40

NS 32

TE 297

FW 9100

O2 6582.331

DP 20L P0

LB .100
GB .100
CX 10.00
CY 30.00
F1 10.0000P
F2 -.499P
HZ/CM 94.527
PPM/CM .262
SR 4833.10
D7 10.0000000
S2 20L 3.80
P0
RGA 0.0
RD 0.0
PW 0.0
DE 86.30
NS 32
DS 2

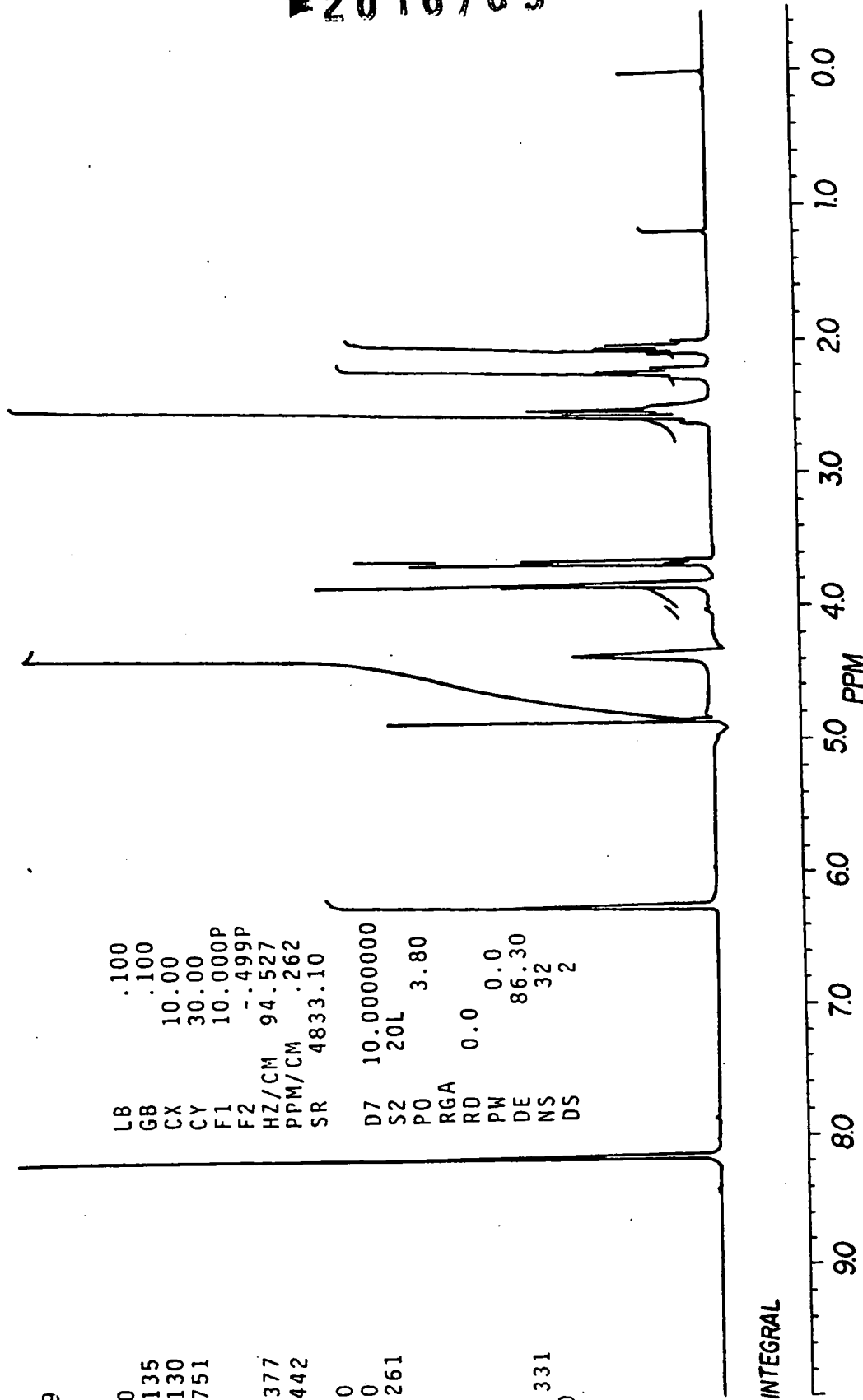


FIG.4

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TGA FOR SODIUM-2',3'-DIDEOXY-2',3'-DIDEHYDROTHYMIDINE

7 SERIES THERMAL ANALYSIS SYSTEM

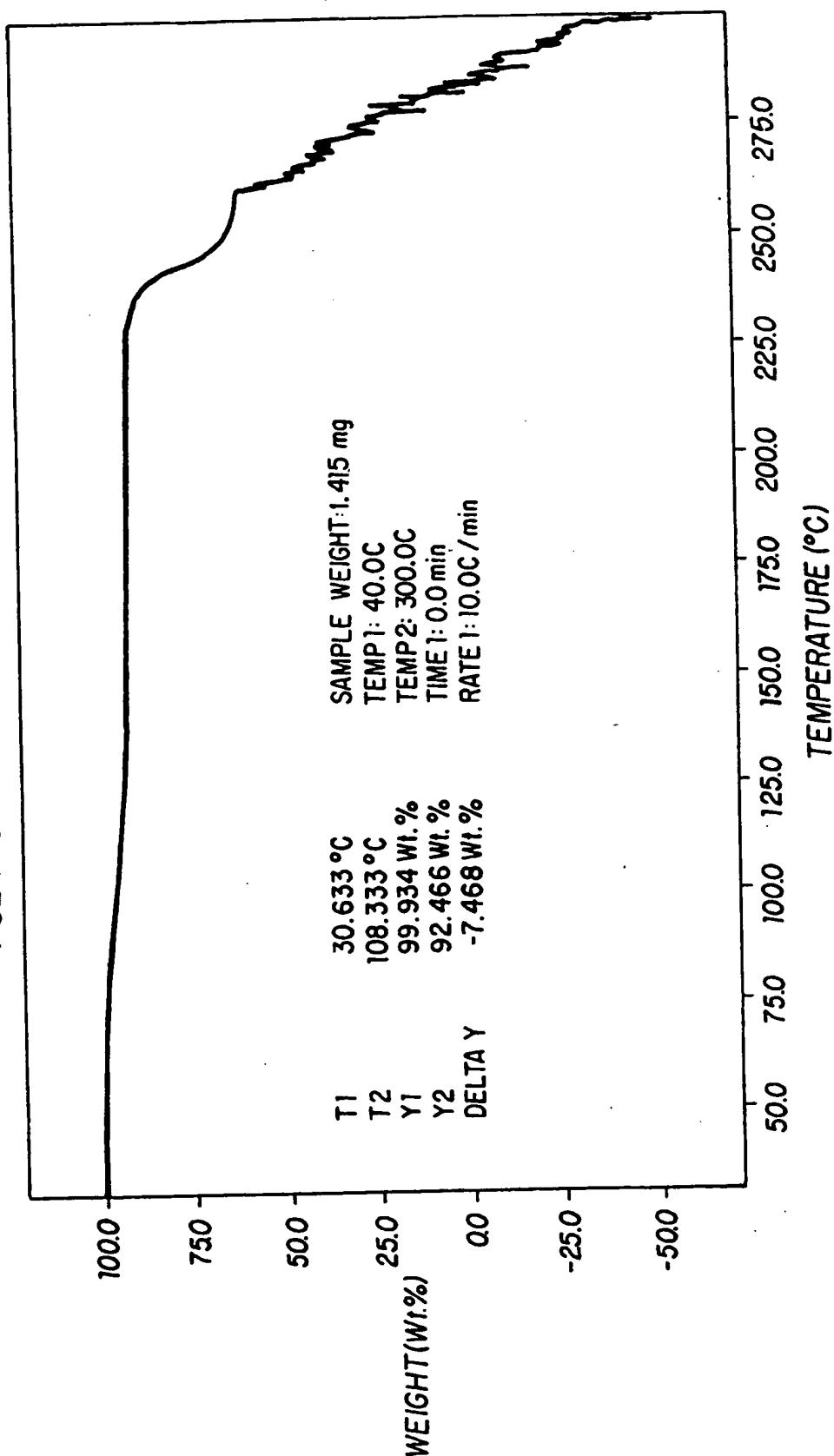


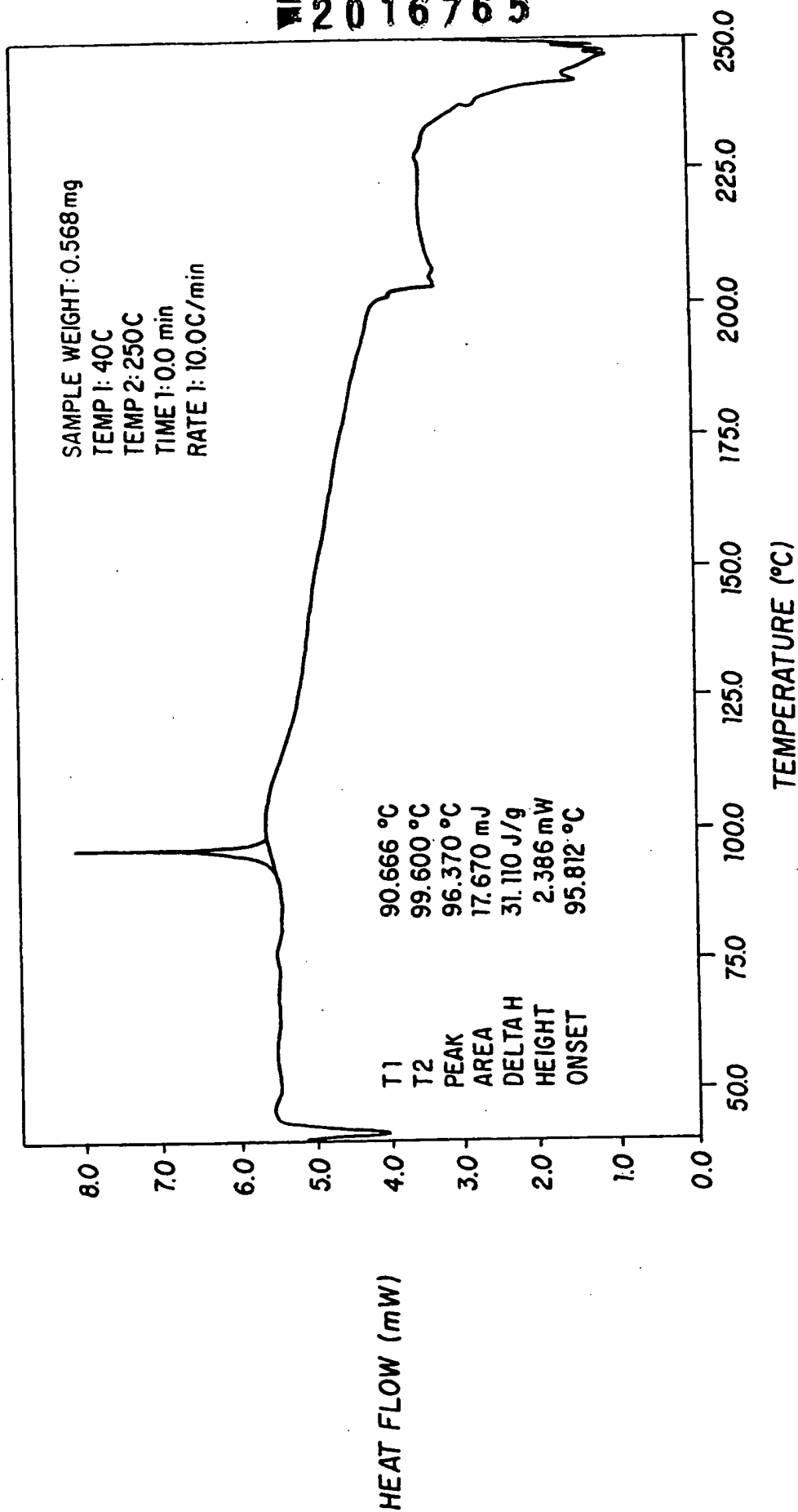
FIG.6

Davidson & Co.
Patent Agents for the Applicant

DSC FOR SODIUM-2',3'-DIDEOXY-2',3'-DIDEHYDROTHYMIDINE.

7 SERIES THERMAL ANALYSIS SYSTEM

SAMPLE WEIGHT: 0.568 mg
TEMP 1: 40C
TEMP 2: 250C
TIME 1: 0.0 min
RATE 1: 10.0C/min



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FIG. 7

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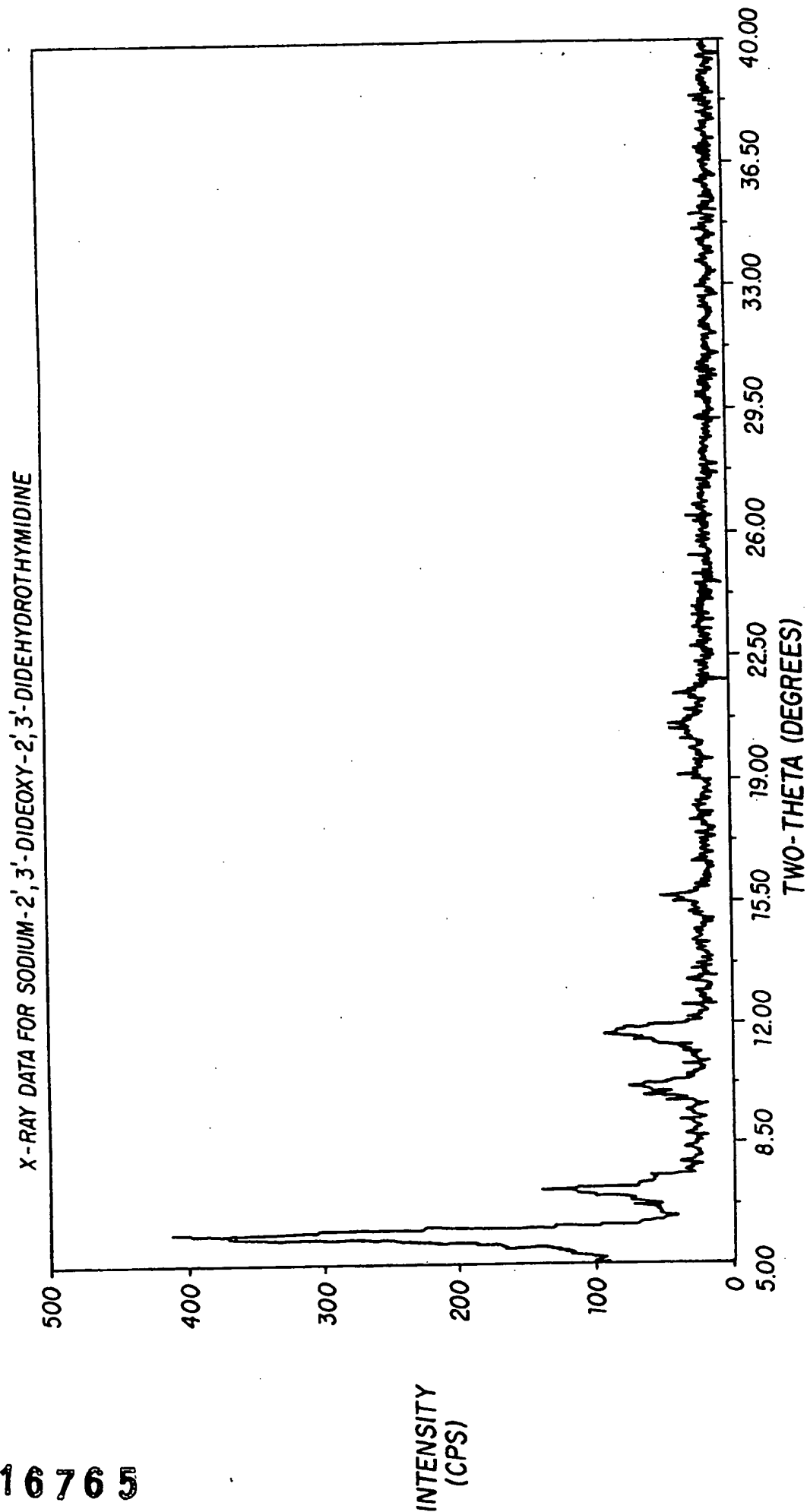


FIG.8

be ... & Cn



SA130S.113

AU PROG:

X45.AU

DATE 20-12-88

TIME 16:46

SOLVENT D2O

SF 360.135

SF0 360.130

O1 6632.751

S1 32768

TD 32768

SW 7246.377

HZ/PT .442

LB .100

GB .100

CX 40.00

CY 30.00

F1 10.000P

F2 -.499P

HZ/CM 94.527

PPM/CM .262

SR 4833.10

PW 0.0

RD 0.0

AQ 2.261

RG 40

NS 32

TE 297

FW 9100

O2 6582.331

DP 20L P0

D7 10.0000000

S2 20L

P0 3.80

RG 0.0

RD 0.0

PW 0.0

DE 86.30

NS 32

DS 2

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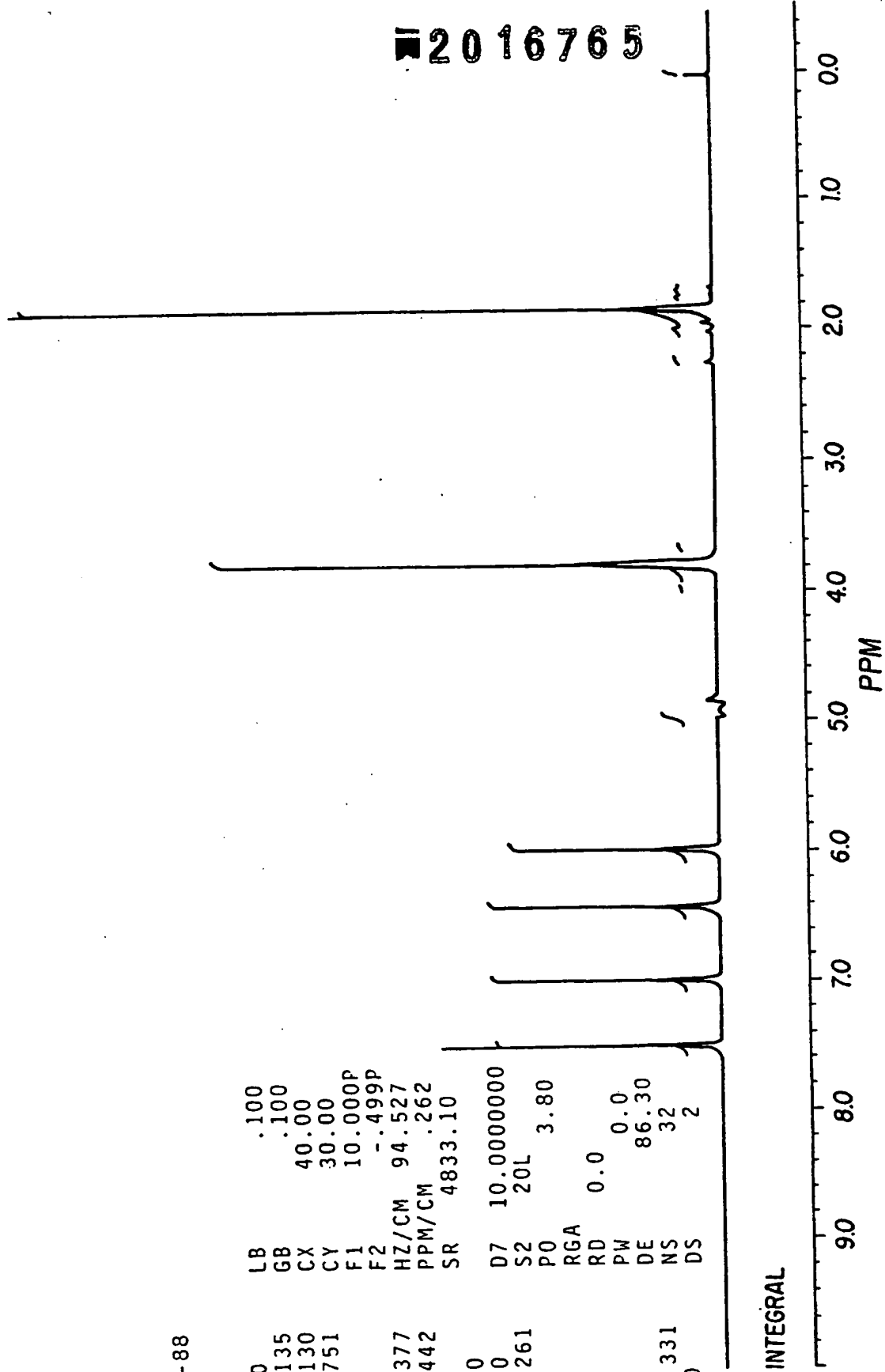


FIG. 9

Acetaminophen

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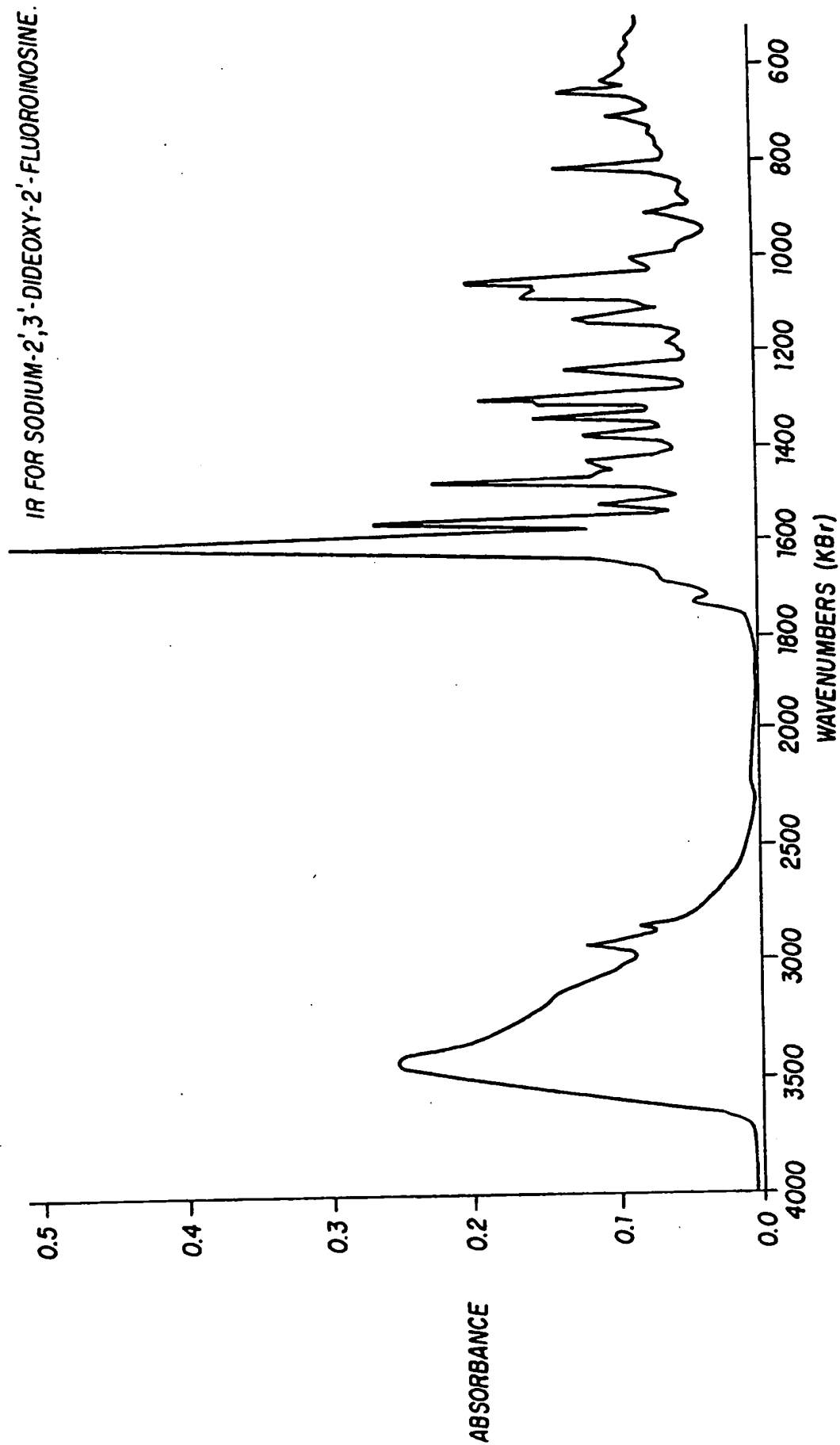


FIG. 10

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NMR FOR SODIUM-2',3'-DIDEOXY-2'-FLUORINOSINE.

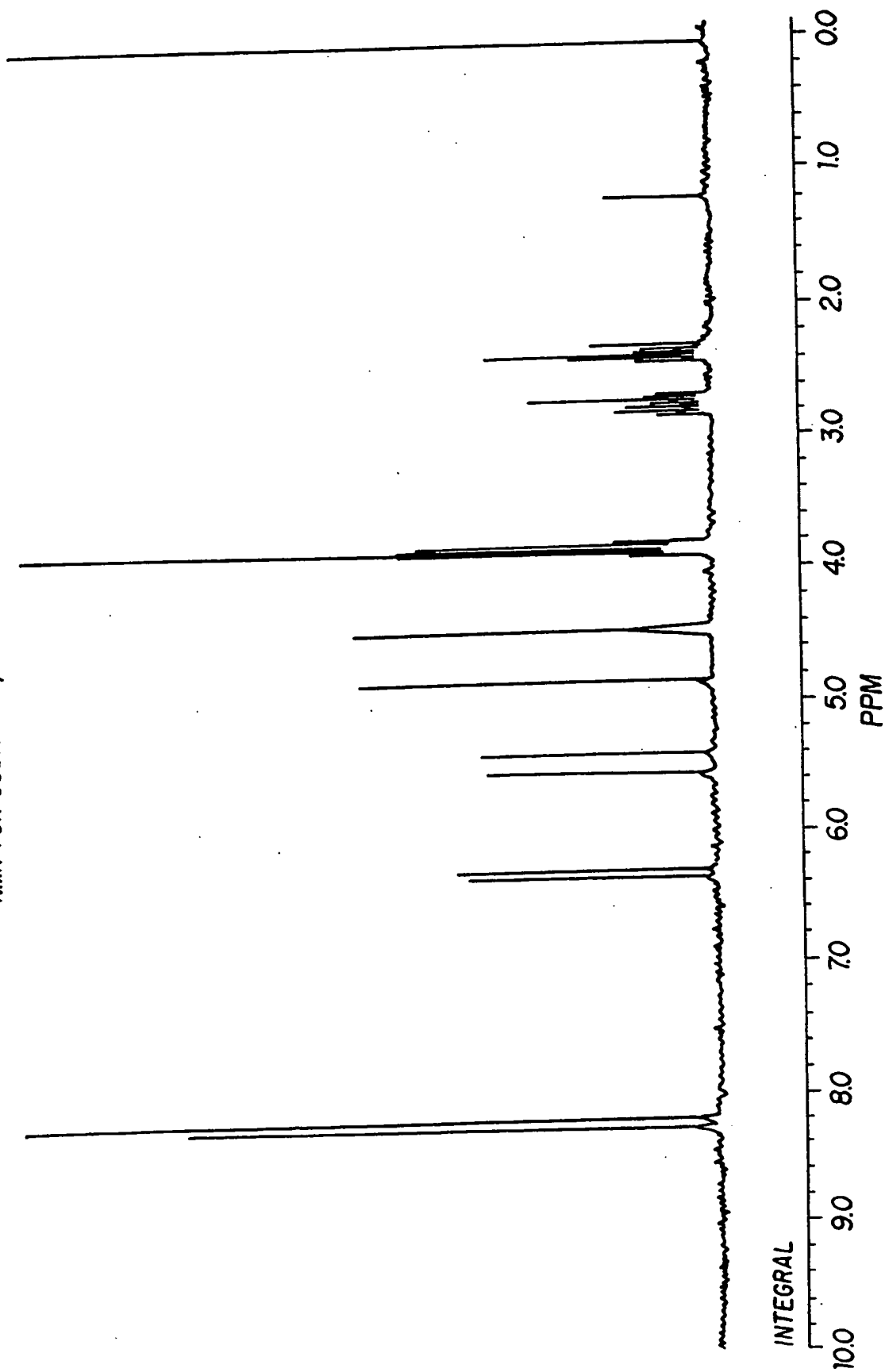


FIG. 17

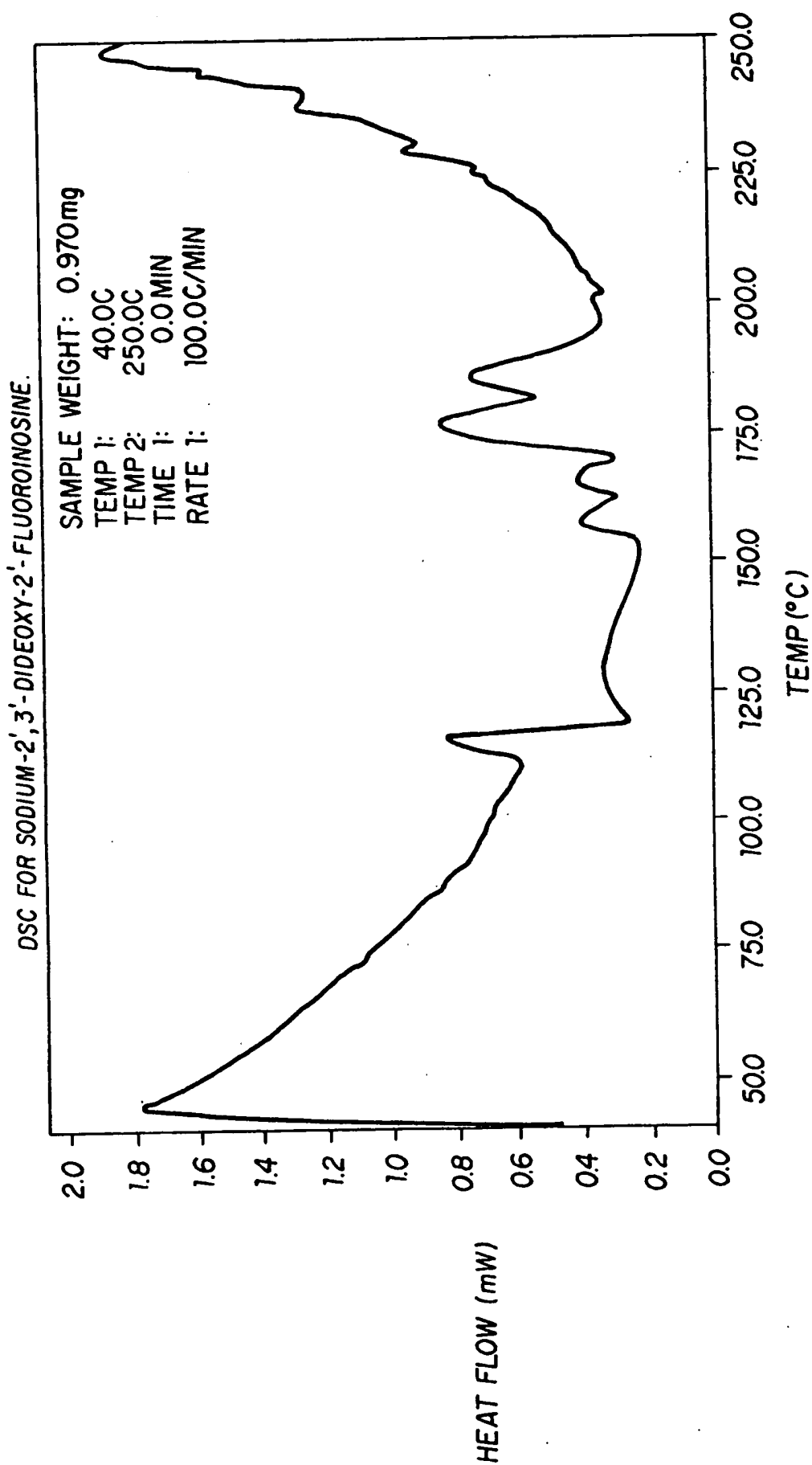


FIG. 12

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TGA FOR SODIUM-2',3'-DIDEOXY-2'-FLUORINOSINE.

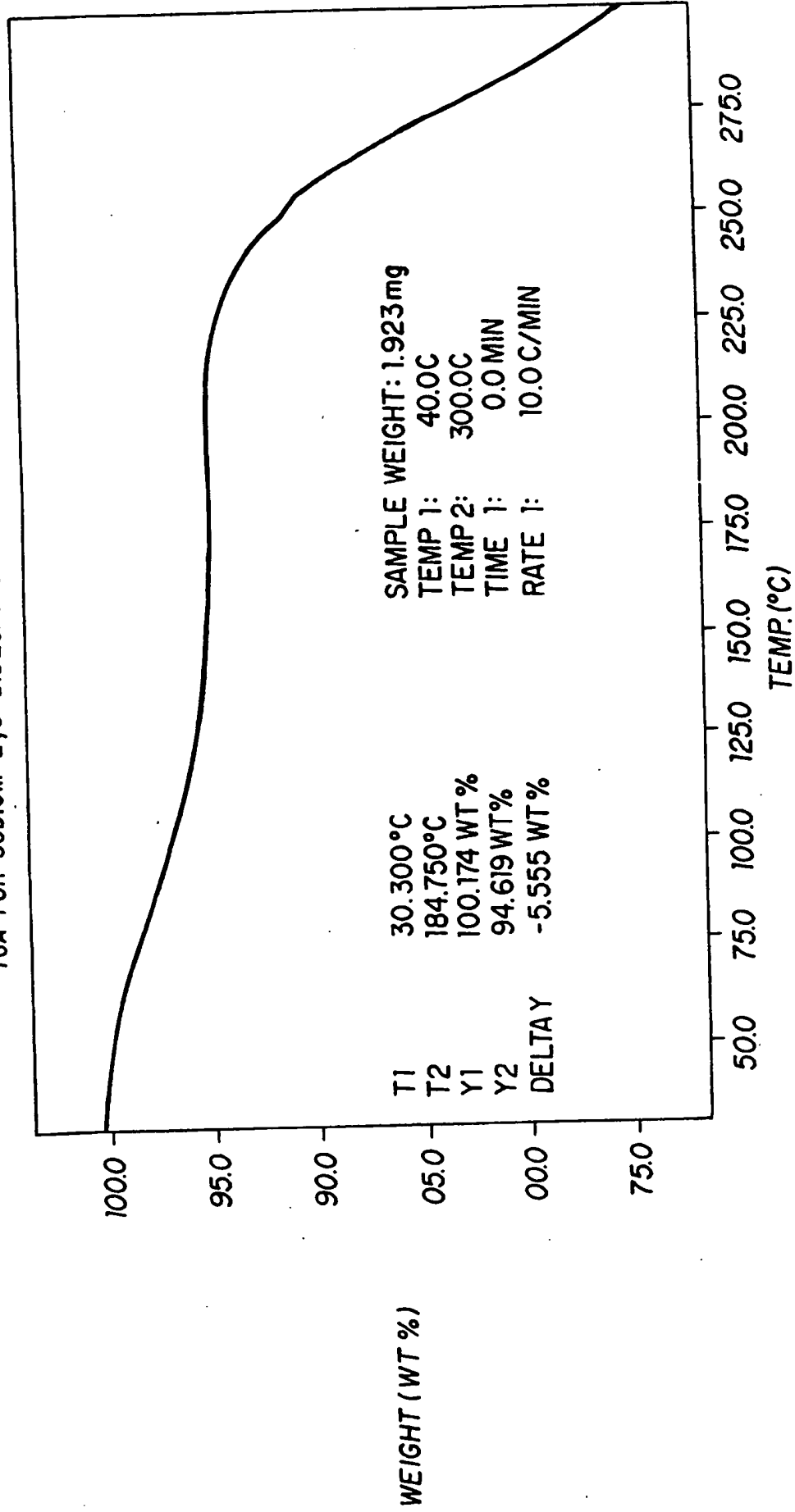


FIG. 13

